Product Development Plan for a mRNA Dengue Vaccine

Mohammad Mainul Ahasan

Incepta Pharmaceuticals Ltd
First isolated in 1943, increasing concern with rapid urbanization

At present, endemic in more than 100 countries

100-400 million infections/year with 96 million clinical manifestation

Almost half of world’s population at risk

Asia represents 70% of global disease burden

Source: WHO, PMID: 21079655
Geographical location, weather, population density contributing together high number of cases

First outbreak reported in 2000, resulted 5551 cases including 93 deaths

Mostly limited to capital Dhaka and very few metropolitan cities

In 2023, distributed all over the country

Source: Directorate General of Health Services, Bangladesh
Dengue is costing tremendous disease burden each year.

In last 24 hours, 263901 hospitalization and 11 deaths.

Three main reason of high disease burden:
- No available vaccine
- No available therapeutics for seriously ill hospitalized patients
- No effective vector control strategy

Source: Directorate General of Health Services, Bangladesh
In 2023, Bangladesh (170 million population) has 2.6 times higher cases than neighboring country India (1.4 billion population).

Among South-East Asia, Bangladesh is experiencing maximum dengue cases and deaths this year.

In the week of 36, US reported maximum number of dengue cases (78), while Bangladesh reported 2575.

Without vaccine research and trials, this situation can bring catastrophic disaster globally.

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1,289.00</td>
<td>-</td>
</tr>
<tr>
<td>Europe (Italy, France &amp; Spain)</td>
<td>74.00</td>
<td>-</td>
</tr>
<tr>
<td>India</td>
<td>94,198.00</td>
<td>91.00</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>247,032.00</td>
<td>1,206.00</td>
</tr>
</tbody>
</table>

Source: CDC; ECDC; DGHS, Bangladesh; NCVBDC, India
For more than 75 years, scientists and product developers have attempted to design and advance safe and efficacious vaccine candidates.

Challenges have been substantial and formidable

- Existence of four DENV types (1–4), each capable of causing infection
- No validated immune correlate of protection
- Animal models do not comprehensively recapitulate the human dengue infection experience
- Immunologic assays are unable to precisely define DENV type-specific immune responses
- Requirement for very large efficacy trials to demonstrate benefit across diverse populations and clinical endpoints
### Dengue Vaccine Development

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Valence</th>
<th>Vaccine formulation</th>
<th>Developer/manufacturer</th>
<th>Evaluation</th>
<th>Adjuvanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengvaxia</td>
<td>2015</td>
<td>Tetravalent</td>
<td>Chimeric viruses YFV/DEN 1–4</td>
<td>Sanofi Pasteur</td>
<td>Licensed</td>
<td>No</td>
</tr>
<tr>
<td>TV003/TV005</td>
<td>2003</td>
<td>Tetravalent</td>
<td>Three genetically attenuated viruses and one chimeric virus</td>
<td>NIAID&lt;sup&gt;a&lt;/sup&gt; and Butantan&lt;sup&gt;b&lt;/sup&gt;</td>
<td>In vivo (phase IIIB)</td>
<td>No</td>
</tr>
<tr>
<td>TAK-003</td>
<td>2006</td>
<td>Tetravalent</td>
<td>Chimeric viruses DEN-2 PDK-53, DEN-1,-3, or -4</td>
<td>Takeda</td>
<td>In vivo (phase I) To be licensed in Indonesia in 2023</td>
<td>No</td>
</tr>
<tr>
<td>TDEN</td>
<td>2017</td>
<td>Tetravalent</td>
<td>Viruses attenuated with passages in PDK cells</td>
<td>WRAIR&lt;sup&gt;e&lt;/sup&gt; and GlaxosmithKline</td>
<td>In vivo (phase I-II)</td>
<td>No</td>
</tr>
<tr>
<td>DPIV</td>
<td>2012</td>
<td>Tetravalent</td>
<td>Purified inactivated viruses (DEN 1–4), Aluminium hydroxide AS01, AS03 or AS04 adjuvants</td>
<td>WRAIR, GlaxosmithKline and PLoCruz&lt;sup&gt;c&lt;/sup&gt;</td>
<td>In vivo (phase I)</td>
<td>Yes</td>
</tr>
<tr>
<td>TVDV</td>
<td>2018</td>
<td>Tetravalent</td>
<td>DNA vaccine based on prM and E protein coding sequences cloned in VR1012 plasmid and co-administered with VAXPECTIN as an adjuvant</td>
<td>U.S. AMRDC&lt;sup&gt;b&lt;/sup&gt;, WRAIR, NMRC and Vical</td>
<td>In vivo (animal and phase I)</td>
<td>Yes</td>
</tr>
<tr>
<td>V180</td>
<td>2018</td>
<td>Tetravalent</td>
<td>Recombinant proteins based on prM and 80% of E protein of DEN 1–4 combined with different adjuvants</td>
<td>Merck and Co.</td>
<td>In vivo (phase I)</td>
<td>Yes</td>
</tr>
<tr>
<td>D5V4</td>
<td>2018</td>
<td>Tetravalent</td>
<td>Virus like particles expressing EDIII of DEN 1–4</td>
<td>International Centre for Genetic Engineering and Biotechnology</td>
<td>In vivo (animal)</td>
<td>No</td>
</tr>
<tr>
<td>E80-mRNA</td>
<td>2020</td>
<td>Tetravalent</td>
<td>mRNA expressing human IgEa and E80 protein packaged into LNP</td>
<td>CAS laboratory of Molecular Virology and Immunology, Institute Pasteur of Shanghai</td>
<td>In vivo (animal)</td>
<td>No</td>
</tr>
</tbody>
</table>

### Platforms
- ✓ Live attenuated
- ✓ Inactivated
- ✓ Protein subunit
- ✓ DNA
- ✓ mRNA

Only **live attenuated virus vaccines** have achieved licensure or reached advanced clinical development.
Dengue Vaccine Development

- **Denvaxia**
  - First licensed vaccine; 20 countries
  - Poor protection in children under age of 9 years
  - Lower protection against DENV1 & 2; predominant Ab response against DENV4

- **TAK-003**
  - Licensed in Indonesia this year to be used in people 4 years of age and older regardless of baseline dengue immune status
  - No protection in seronegative recipients against all dengue and hospitalized dengue due to DENV3
  - No conclusive data for DENV4 due to low event numbers during trial

- **LATV TV003/TV005**
  - Initiated Phase 3 study in 2016 with 16,000 volunteers in Brazil
  - Efficacy data is only available for DENV1 (89.5%) and DENV2 (69.6%) due to the low circulation of types DENV3 and 4 during the trial

A more effective vaccine that can generate heterotypic nAb against all four DENV serotypes is still needed
Recent advances have updated the mRNA vaccine development of many flaviviruses.
Partnership with Prof. Drew Weissman Lab at University of Pennsylvania

New R&D lab dedicated for mRNA by Q1 2024

mRNA GMP production facility in design phase

Capability to produce raw materials for mRNA production
- T7 RNA polymerase
- dNTPs
- Cap analog

Dengue Vaccine Development
Dengue Vaccine Development

DENV mRNA vaccine development timetable

**Phase I**
- Conceptualization: Project goals & schedule established
- Immunogens selection & design: Bioinformatics, Experiment design, Project kickoff
- Vector generation

**Phase II**
- mRNA vaccine production: mRNA production, Expression & QC assessment
- mRNA vaccine encapsulation: Encapsulation in lipid nanoparticles (LNPs)
- Pre-clinical studies: Mice & monkey immunization, DENV challenge

**Phase III**
- Data acquisition and analysis: Ab (Total & nAb), & T cell responses, ADE assessment

*in progress*
DENG mRNA vaccine project team

**Project leader:** Xiomara Mercado-López, Ph.D., MPH

**Research technicians:**
- Wendy Bonilla-Acosta, M.S.
- Valeria Bornacelli, M.S.
- Bangladesh had hosted **world largest measles-rubella vaccination campaign**

- **High vaccine acceptance rate** among common people. Ranked among top 15 countries for COVID-19 vaccination

- **Vaccine research and manufacturing facility** at disposal (e.g. Incepta Pharmaceutical Ltd.)

- Globally recognized **CRO for trials** (e.g. icddr’b)
Acknowledgements

- University of Pennsylvania
  - Prof. Drew Weissman
  - Dr. Xiomara Mercado-López

- Imperial College London
  - Prof. Robin Shattock

- WHO/MPP/AfriGen
THANK YOU

THANK YOU

THANK YOU